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Naturally occurring and synthetic inhibitors of NF-kappaB functions.

Umezawa K, **Ariga A**, **Matsumoto N**.

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Nuclear factor (NF)-kappaB is a transcription factor that induces the immunoglobulin kappa chain, cytokines such as interleukin (IL)-1, IL-2, IL-6, IL-8, tumor necrosis factor (TNF)-alpha and interferon gamma, and cell adhesion proteins. It also induces anti-apoptotic proteins, and inhibits TNF-alpha and anticancer drug-induced apoptosis. Therefore, NF-kappaB function inhibitors may be useful as anti-inflammatory and anticancer agents. Microbial products such as panepoxydone, cycloepoxydon and gliotoxin are known to inhibit activation of NF-kappaB. We have designed and synthesized new NF-kappaB inhibitors from the structure of an antibiotic, epoxyquinomicin C. The designed compound, DHM2EQ, inhibited TNF-alpha-induced activation of NF-kappaB and showed a therapeutic effect in mouse rheumatoid arthritis model.

Publication Types:
- Review

PMID: 11200499 [PubMed - indexed for MEDLINE]

☐ **2:** Expert Opin Investig Drugs. 2001 Mar;10(3):467-76. Related Articles, Links

The immunotherapeutic potential of melatonin.

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The interaction between the brain and the immune system is essential for the adaptive response of an organism against environmental challenges. In this context, the pineal neurohormone melatonin (MEL) plays an important role. T-helper cells express G-protein coupled cell membrane MEL receptors and, perhaps, MEL nuclear receptors. Activation of MEL receptors enhances the release of T-helper cell Type 1 (Th1) cytokines, such as gamma-interferon (gamma-IFN) and IL-2, as well as of novel opioid cytokines. MEL has been reported also to enhance the production of IL-1, IL-6 and IL-12 in human monocytes. These mediators may counteract stress-induced immunodepression and other secondary immunodeficiencies and protect mice against lethal viral encephalitis, bacterial diseases and septic shock. Therefore, MEL has interesting immunotherapeutic potential in both viral and bacterial infections. MEL may also influence haemopoiesis either by stimulating haemopoietic cytokines, including opioids, or by directly affecting specific progenitor cells such as pre-B cells, monocytes and NK cells. MEL may thus be used to stimulate the immune response during viral and bacterial infections as well as to strengthen the immune reactivity as a prophylactic procedure. In both mice and cancer patients, the haemopoietic effect of MEL may diminish the toxicity associated with common chemotherapeutic protocols. Through its pro-inflammatory action, MEL may play an adverse role in autoimmune diseases. Rheumatoid arthritis patients have increased nocturnal plasma levels of MEL and their synovial macrophages respond to MEL with an increased production of IL-12 and nitric oxide (NO). In these patients, inhibition of MEL synthesis or use of MEL antagonists might have a therapeutic effect. In other diseases such as multiple sclerosis the role of MEL is controversial. However, the correct therapeutic use of MEL or MEL antagonists should be based on a complete understanding of their mechanism of action. It is not yet clear whether MEL acts only on Th1 cells or also on T-helper Type 2 cells (Th2). This is an important point as the Th1/Th2 balance is of crucial importance in the immune system homeostasis. Furthermore, MEL being the endocrine messenger of darkness, its endogenous synthesis depends on the photoperiod and shows seasonal variations. Similarly, the pharmacological effects of MEL might also be season-dependent. No information is available concerning this point. Therefore, studies are needed to investigate whether the immunotherapeutic effect of MEL changes with the alternating seasons.

Publication Types:
- Review

PMID: 11227046 [PubMed - indexed for MEDLINE]

☐ **3:** Ann N Y Acad Sci. 2000;917:825-34. Related Articles, Links

Full Text Ann N Y Acad Sci

Perturbations of arginine vasopressin secretion during inflammatory stress. Pathophysiologic implications.

Chikanza IC, **Petrou P**, **Chrousos G**.

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Pro-inflammatory cytokines, such as interleukin-1 beta (IL-1 beta), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF alpha), released from inflammatory foci, can activate the hypothalamus to produce corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP). These hypothalamic peptides in synergy increase ACTH production by the pituitary gland and hence corticosteroid (CS) secretion by the adrenal cortices. CS dampens inflammation. The pituitary also produces prolactin (PRL), which is pro-inflammatory, and macrophage inhibitory factor (MIF), which by counteracting the anti-inflammatory and immunosuppressive effects of CS, is pro-inflammatory. Lewis rats develop a variety of induced-autoimmune inflammatory conditions, such as streptococcal cell wall arthritis, whereas the histocompatible F344 Fisher rats are resistant to this condition. Lewis rats have a defective hypothalamic-pituitary adrenal (HPA) response to a variety of hypothalamic stimuli, but have augmented systemic secretion of AVP. Patients with rheumatoid arthritis (RA) have deficient CS with exaggerated PRL responses to inflammatory stimuli. Within inflammatory foci, CRH is pro-inflammatory. AVP, which augments autologous mixed lymphocyte reactions, can replace the IL-2 requirement for gamma IFN production by T cells via V1a receptors, and potentiates primary antibody responses, is also pro-inflammatory. Lewis rats have significantly high plasma levels, hypothalamic content, and in vitro release of AVP in comparison to the inflammatory disease-resistant Fischer rats. Immunoneutralization of AVP attenuates inflammatory responses. In Sprague-Dawley rats, AVP potentiates PRL secretion. Preliminary studies in patients with RA have shown that the circulating levels of AVP are significantly increased, which might be a compensatory response to low CS levels or a result of elevated levels of IL-6 in these patients but could nevertheless contribute to rheumatoid inflammation. A similar observation has been made in patients with ankylosing spondylitis.

Publication Types:
- Review

PMID: 11268412 [PubMed - indexed for MEDLINE]

☑ **4:** Pol Merkur Lekarski. 2001 Jun;10(60):477-9. Related Articles, Links

[Current opinions on immunological processes in rheumatoid arthritis during pregnancy]

[Article in Polish]

Biesiada L, Krasomski G, Tchórzewski H.

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The essential in pathogenesis of RA is induction of incorrect immunological response against synovial and connective tissue antigens, which depends of CD4+ T-cells activation by specific antigen. This stimulation leads to releasing Th1 lymphokines. The most important cytokine is TNF-alpha. An increased level of TNF-alpha, IL-1, IL-6, GM-CSF, IL-8 was observed in patients with RA. PDGF, FGF, TGF, C-X-C a chemokines (IL-GRO-alpha, ENA78) and CCb chemokines (RANTES, MCP1 MIP1 alpha) are also involved in synovial hyperplasia in RA. During a pregnancy a clinical improvement in women with RA is frequent. The reason of this fact is probably connected with Th2 predominance (IL-4, IL-10) caused by presence of fetal tissues. Specific, cell-mediated immunity is suppressed and changed to Th2 by progesterone

Progesterone stimulates T cells to PIBF production, which decreases NK activity. Th2 cytokines (Il-6, IL-10, IL-13, TGF) are expressed on decidua and inhibit secretion of Th1 cytokines (IL-2, INF gamma, TNF-alpha, IL-1 alpha, IL-1 beta). Immunosuppression caused by pregnancy probably decreases inflammatory and destructive reactions in tissues women with RA. The first attack of this disease frequently observed during puerperium is connected with a high level of prolactin and a low of estrogens, which causes a increased release of IL-2 and has a main influence on initiation and increasing of inflammatory process in RA.

Publication Types:
- English Abstract
- Review

PMID: 11503269 [PubMed - indexed for MEDLINE]

☑ **5:** Clin Lymphoma. 2000 Nov;1 Suppl 1:S37-40. Related Articles, Links

DAB(389)IL-2 (denileukin diftitox, ONTAK): other potential applications.

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DAB(389)IL-2 (denileukin diftitox, ONTAK) is an interleukin-2 receptor (IL-2R)-specific ligand fusion protein that may potentially be selective for IL-2R-expressing malignancies. The activity of DAB(389)IL-2 in the treatment of cutaneous T-cell lymphoma has established the feasibility of utilizing such a targeted therapeutic in disseminated disease with acceptable toxicity. Data from the phase I trial suggest that the definition of activity in other cancer types, including other non-Hodgkin's lymphomas (NHL), is warranted. Three NHL patients in this study responded, two of whom had follicular lymphomas, with the third having a primary intermediate-grade B-cell NHL that was refractory to chemotherapy and stem cell transplant. This patient has remained in complete remission over 3 years after treatment with DAB(389) IL-2. Patients treated to date have had IL-2R-positive tumors, but this remains a very complex clinical issue. The need for a threshold level of receptor expression, the difficulty in obtaining representative tissue, the lack of an assay that accurately reflects high-affinity receptor, and the potential difficulty of observer variability in evaluating the assays should point us toward examining response rates in cancer patients where IL-2R cannot be detected or is unknown. The potential to target the high-affinity IL-2R supports the development of this agent in transplantation and in autoimmune diseases. Targeting IL-2R-expressing lymphocytes may be an effective strategy for the prevention of graft rejection and to treat or prevent graft-versus-host disease. DAB(389)IL-2 has been examined in clinical trials of psoriasis and rheumatoid arthritis and has shown promising results. The potential utility in other autoimmune disorders is unknown, but diseases such as systemic lupus, scleroderma, and vasculitis also may be effective candidates for such ligand fusion therapy.

Publication Types:
- Review

PMID: 11707862 [PubMed - indexed for MEDLINE]